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Alprazolam and Cognitive Behavior Therapy in Treatment of Panic Disorder

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Abstract: Panic is an often incapacitating and chronic disorder. Cognitive behaviour therapy (CBT) and alprazolam have been shown to be effective in the treatment of panic disorder. Patients who met the DSM-III-R criteria for panic disorder, were randomized and given 16 weeks of double-blind treatment with CBT (n=16), or alprazolam of up to 6 mg/day (n=18). The 17-item HAM-D and HAM-A scales were administered to all the subjects before and after treatment, which took place over 16 weeks, and the changes in the scores were analyzed. The patients' anxiety levels and numbers of panic attacks were assessed at the beginning of treatment, and then at weeks 4,8,12 and 16 by means of self-monitoring. On the basis of HAM-D, HAM-A, anxiety level, and panic number, the CBT and alprazolam groups showed a significant improvement at the end of treatment. When compared to each other, the groups showed no significant differences at the end of the treatment. In the last month, 10/16 (62.5%) of the CBT patients and 11/18 (61.1%) of the alprazolam patients were panic-free.

Key Words: Alprazolam, Cognitive behavior therapy, Panic disorder.

Introduction

Panic disorder is a common anxiety disorder associated with a great deal of distress as well as marked social and occupational disability (1,2). Such patients are over-represented with regard to the use of medical services, such as emergency room visits, the number of visits to physicians and the use of psychotropic medications (3,4,5,). In addition, their rate of attempted suicide has been reported to be either greater to that of the general population or equal to that of patients suffering from major depression (6,7,8).

Clinical evidence suggests that cognitive-behaviour therapy (CBT) is an effective treatment for panic. For example, Gitlin et al. reported that 10 out of 11 patients receiving CBT were not panicking by the end of treatment (9). Beck, Ost, Craske have also reported nearly total elimination of panic in patients suffering from panic disorder using either cognitive behavioral or behaviorally-based relaxation treatments (10,11,12).

In the 1980s, a new class of benzodiazepines, the triazolobenzodiazepines, became available. One member of that class, alprazolam, has been reported to be effective in the treatment of panic disorder (13,14).

To our knowledge, few reports have compared the efficiency of both treatment in patients with panic disorder. In view of the effectiveness of this CBT and of alprazolam in panic disorder, the purpose of this study was to evaluate the effectiveness of each treatment.

Materials and Method

Subjects: Patients were drawn from patients attending the psychiatry clinic. All had been given a diagnosis of panic disorder with mild or no agoraphobic avoidance, using DSM-III-R criteria. Only patients with at least four panic attacks within a four-week period, or those experiencing one or more attacks followed by a period of at least a month of persistent fear of another attack were included.

The general exclusion criteria were as follows: age below 18 or above 65 years, current drug or alcohol abuse/dependency, principal diagnosis of major depression, and any signs of psychosis or organic brain syndrome. Finally, subjects were excluded if they had begun taking benzodiazepines or antidepressants within the previous six months.

At the onset of treatment, the subjects comprised 40 patients with panic disorder.

The patients were treated with either CBT or alprazolam for two months, and then followed for two months without CBT and alprazolam.

Measures: Clinical assessment measures consisting of the Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Rating Scale for Depression (HAM-D) were administered to all subjects before and after treatment, and the changes in the scores were analyzed.

A self-monitoring measure was administered at the beginning of treatment and assessed at 4-week periods throughout treatment. Patients monitored their current levels of anxiety on a 0-to-8-point visual analogue scale, four times a day (morning, afternoon, evening and bedtime), stating whether or not they experienced panic (patients were instructed and trained to define and differentiate a panic attack from episodes of generalized anxiety). The data from the visual analogue scale served to measure the anxiety level and panic number

Alprazolam treatment group: Patients received 1mg doses of alprazolam (1 or 2 mg) up to four times daily. Medication was gradually increased until the maximum benefit was achieved or dose-limiting side effects occurred. Patients began taking one tablet per day (for two days) and then this was increased to two tablets (for three days), three tablets (for four days), four tablets (for four days), five tablets (for four days), and then six tablets per day on day 18. When side effects were reported, these increases in medication were slowed or the dose was reduced. Every effort was made to achieve a dosage of six tablets per day.

Patients were given an explanation of their condition, including what could be expected of the medication. No other centrally active medications were administered during the trial.

At the beginning of the 9th week of treatment, the psychiatrist began to taper the doses of alprazolam at a rate no faster than one tablet every 3 days. The psychiatrist continued meeting patients until they had stopped taking medication completely.

CBT group: The treatment consisted of a 2-month course of CBT. The patients received 8 individual sessions of CBT for panic disorder in weekly meetings. Exposure plus cognitive restructuring were applied in the case of these patients. Treatment comprised a rationale and education concerning panic disorder, the components of anxiety and emphasized exposure to somatic cues. Cognitive approaches were also included. In cognitive

therapy, we helped the patients to identify and modify their negative thoughts. In addition, the patients were encouraged to expose themselves to situations or activities which they were avoiding. They were also encouraged to modify behaviours which occur once symptoms have started and which maintain a patient's belief that certain symptoms are highly dangerous.

Results

Out of 40 initial patients, 34 patients completed the study, and 6 patients dropped out. A higher rate of drop out was observed in the CBT group than in the other group. Two patients out of 20 (10%) dropped out of the alprazolam group, while 4 out of 20 (20%) dropped out of the CBT group.

A t-test analysis on these dorp-out frequencies showed no significant differences between the CBT and alprazolam group (t=1.03,p=0.314).

Patients who dropped out of the study were questioned about their reasons. Of the 4 patients who dropped out of the CBT group, 2 developed intense panic attacks in the 1st week of the treatment, causing them to drop out of the study. Two were unavailable for interview after the second week of treatment. The 2 subjects who dropped out of the alprazolam treatment group stated that they disliked the side effects of the medication in the 1 st week of treatment (1 reported over-sedation, and 1 reported suicidal ideation).

In the CBT group, 9 men (56%) and 7 women (43%) completed the study. The mean age was 30.81 years. In the alprazolam group, 6 men (44%) and 12 women (56%) completed the study. The mean age was 31.44 years. The mean age difference between the groups was not significant (F=0.574, df=32, t=-0.234, p>0.05).

In the CBT group (16 patients), the mean score on the Hamilton Depression Scale at week 0 was 12.06 (range, 2 to 45), with only 5 patients (31.2%) scoring values above 14. In the alprazolam group (18 patients), the mean score on the Hamilton Depression Scale at week 0 was 10.83 (range, 2 to 40), with only 6 patients (33.3%) scoring in the range above 14.

In the study intake, no statistical difference between the two groups in the average HAM-D and HAM-A scores were found using the Mann-Whitney test (z=-0.657, p>0.528), (z=-0.346, p>0.746).

In terms of HAM-D scores, the CBT and alprazolam groups showed a statistically significant improvement on the Wilcoxon signed rank test at the end of the 4 months,

and there was no difference between the groups on the Mann-Whitney test (Table 1).

The scores on HAM-A were found to have decreased significantly at the end of the treatment in the cognitive-behavior and alprazolam groups on the Wilcoxon signed rank test. This is described in Table 1. The differences in anxiety scores in both groups found at the end of the study were compared, but the decrease in anxiety scores was not found to be significant on the Mann-Whitney test. This is described in Table 1.

In the CBT group, anxiety level (on the 0-8 scale) from baseline to end point was compared using the Friedman test and the decrease in anxiety level was found to be significant (x^2=50.888, df=4, p<0.0001). Similarly, in the alprazolam group the decrease in anxiety level was found to be significant on the Friedman test (x^2=30.499, df=4, p<0.0001).

When the treatments were compared in terms of anxiety level, it was found that most improvement occurred with alprazolam in the first month, and then with CBT in the third and fourth months. This is described in Table 2.

Both CBT and alprazolam significantly reduced panic frequency at the end of the treatment according to the results of the Friedman test (x^2=26.160, df=4, p<0.0001), (x^2=16.987, df=4, p<0.002). In the end-point analysis, 11/18 (61.1%) of the alprazolam patients and 10/16 (62.5%) of the CBT patients had no panic attacks in the last month. The number of panic attacks did not show any statistically significant differences between the two groups throughout the study (except in the first month) on the Friedman test This is described in Table 3.

Table 1.   The difference in anxiety and depression scores in both groups.

	Before treat. anxiety score		after treat. anxiety score			Before treat. depression score		After treat. depression score		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Cog.	31.18	4.13	20.37	7.57	z=-3.239 P<0.001	12.06	6.54	8.43	2.98	z=-2.332 p<0.02
Alp.	31.77	4.79	23.27	5.86	z=-3.030 P<0.02	10.83	6.13	8.66	3.36	z=-2.078 p<0.04
			z=-1.491,		p>0.144			z=-0.208,		p>0.851

Table 2.   Anxiety levels reported by each group.

	Cog. treatment group		Alp. treatment group		
	Mean	SD	Mean	SD	
Baseline	12.06	5.91	11.88	4.02	z=-0.104, p>0.932
1-Month	18.81	8.43	5.38	3.83	z=-4.199, p<0.001
2-Month	6.43	4.64	9.00	4.10	z=-1.800, p>0.075
3-Month	3.00	4.13	5.33	3.32	z=-2.501, p<0.01
4-Month	0.68	0.94	1.94	1.79	z=-2.320, p<0.025

Table 3.   Number of panic attacks.

	Cog. treatment group		Alp. treatment group		
	Mean	SD	Mean	SD	
Baselinea	93	68	94	72	z=-0.19, p>0.97
1-Month	1.37	1.08	22	42	z=-3.405,p<0.001
2-Month	18	40	44	61	z=-1.326,p>0.3
3-Month	31	60	27	46	z=-0. 067,p>0.96
4-Month	12	34	16	38	z=-0.337,p>0.851

Discussion

When a person is anxious, there are three different components to his/her reaction: a physiological component (e.g., increased heart rate, sweating, muscle tension), a behavioural component (e.g. avoidance, attempts to escape), and a cognitive component (negative thoughts, such as "I am going to collapse", "I cannot cope"). The relative strength of these components varies from person to person, but it is common for people to experience a physiological change, followed by a negative thought, which increases the physiological reaction, producing a vicious circle. To break this vicious circle we encouraged the patients to focus on and to expose themselves to the physiological reaction which they were avoiding. It was also important to modify behaviours which occur once symptoms have started and which maintain the patients' belief that certain symptoms are highly dangerous.

Cognitive-behavioral approaches are thought to have an impact on panic and anxiety by affecting cognitive rather than somatic symptoms. In this study, however, we saw that patients' somatic sensations were reduced and we considered that this was related to cognitive change concerning the disease in the patients. The cognitive model of panic states that individuals experience panic attacks because they have a relatively enduring tendency to interpret a range of bodily sensations in a catastrophic fashion. Sensations which are misinterpreted are mainly those which can be involved in normal anxiety responses (e.g. palpitation, breathlessness, dizziness). The catastrophic misinterpretation involves perceiving these sensations as indicative of an immediately impending physical or mental disaster. For example, a patient who was preoccupied with the idea he may be suffering from cardiac disease avoided exercise whenever he noticed palpitations. He believed that this avoidance helped to prevent him from having a heart attack. However, as he

had no signs of cardiac disease, the real effect of the avoidance was to prevent him from learning that the symptoms he was experiencing were innocuous.

In this study, as the patients were prevented from avoiding such situations, their negative thoughts about body sensations changed, and these changed body sensations changed their cognition of the disease.

Panic attacks were eliminated in a very large percentage of patients (in the CBT group, 62.5%; in the alprazolam group, 61.1%). These findings are similar to reports of long-term clinical outcome studies testing CBT for panic disorder in which nearly 70% of patients were found to be panic-free (12, 15). These findings indicate that CBT is an effective short-term treatment of panic disorder. Studies comparing the long-term treatment and short-term treatment of CBT in patients who have panic disorder are needed to facilitate decision-making with relation to therapy.

At the end of study, improvement in the anxiety and depression scores of the two groups were observed. In the number of panic attacks and in the anxiety level significant differences favoring alprazolam over CBT were observed in the first month of the study. In the patients' reported anxiety levels, significant differences favoring CBT over alprazolam were observed in the third and fourth months. It is important to emphasize that significant improvements observed clinically in the first month in the alprazolam group were probably due to the action of the alprazolam. This observation is consistent with a slower onset of effects with CBT than with alprazolam (16).

These findings, suggest that it might be beneficial to start patients on alprazolam with a therapeutic contract in order to withdraw them from alprazolam as CBT progresses. In this way, patients are protected from the long-term therapy risk of alprazolam.

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